UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	7

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applic...(s)
09/487,851	Levy et al.
Examiner	**Group Art Unit**
Gai (Jennifer) Mi Lee	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-64 is/are pending in the applicat

Of the above, claim(s) 40-64 is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-39 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Preliminary Amendment filed May 23, 2000 in Paper No. 5 is acknowledged. Claims 40-64 are canceled without prejudice to inclusion of the subject matter of these claims in one or more subsequently filed patent applications. **Claims 1-39 are under current examination.**

Applicants' Information Disclosure Statement, filed June 22, 2000, Paper No. 6, has been considered.

Claim Objections

Claim 33 is objected to because of the following informalities: Claim 33 is improperly depended onto itself. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the

art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte Forman*, (230 USPQ 546 (Bd Pat. App. & Int. 1986)).

The claimed invention is directed to a method of alleviating a disease or disorder in an animal cell comprising locally delivering to the cell a reverse gene therapy vector comprising a promoter operably linked with a nucleic acid encoding a therapeutic gene product which is usually only expressed in cells of an abnormal tissue that is not afflicted with the disease or disorder, whereby delivery of the vector to the affected cell and expression of the gene product therein alleviates the disease or disorder (claims 1 and 2). In particular, the protein is selected from the group consisting of a defective HERG protein, an apoptosis-induced protein, transcription factor E2F1, tenascin C, bone morphogenic protein, a protein involved in synthesis of a glycosaminoglycan, a dominant negative mutant receptor protein, transcription factor NF-Atc, a mutant fibroblast growth factor receptor protein, and a degradation resistant collagen protein wherein the protein is a defective HERG such as HERG (A561V) protein (claims 3-5). In further embodiment, the reverse gene therapy vector is selected from the group consisting of naked DNA, a plasmid, a condensed nucleic acid, and a virus vector comprising a nucleic acid wherein the vector is a virus vector such as adenovirus vector, a retrovirus vector, an adeno-associated virus vector and a herpes virus vector or a condensed nucleic acid or a plasmid operably linked to a constitutive promoter (i.e. CMV), a tissue-specific promoter, more specifically a cardiac tissue-specific promoter selected from the group consisting of an ANF promoter or an α-MyHC promoter (claims 6-17). In further embodiment, the reverse gene

therapy vector further comprises a pharmacological agent-sensitive enhancer such as phorbol ester-sensitive enhancer or Cre-recombinase-sensitive site (claims 18-20). In further embodiment, the reverse gene therapy vector is delivered to the cell in a sustained-release manner selected from a group consisting of a particle comprising the vector, a microparticle comprising the vector, a nanoparticle comprising the vector, an implantable device having a surface coated with a matrix comprising the vector, and a bulk material comprising the vector wherein the implantable device comprises an electrode located in close proximity to a myocardial tissue of the animal and wherein the myocardial tissue is right atrial myocardium (claims 21-24). In further embodiment, the cell is located outside the body of the animal wherein the cell is cultured cell or wherein the cell is subsequently returned to the body of the animal from which the cell was obtained or wherein the cell is subsequently returned to the body of a second animal other than the animal from which the cell was obtained (claims 25-28). In further embodiment, the cell is located inside the body of the animal wherein the cell is located in a cardiac tissue of the animal wherein the cell is a myocardial cell of a right atrial myocardium cell of the crista terminalis and wherein the animal is afflicted with re-entry atrial flutter wherein the therapeutic defective HERG is HERG (A561V) protein operably linked to a cardiac tissue-specific promoter selected from the group consisting of an ANF promoter and an α-MyHC promoter (claims 29-38).

The specification teaches that the rate of release of ibutilide from the electrode in dogs which demonstrated the site-specific therapy directed at the right atrial myocardium can be

effective to suppress re-entrant atrial flutter (pages 41-42). The specification further teaches a method of locally deliver a nucleic acid vector comprising a defective HERG protein to the right atrium of dogs in order to effect site specific overexpression of HERG (A561V) at that site. See Example 2. The specification teaches that the goals of these dog studies are to investigate DNA-containing nanoparticle delivery techniques and early events involved in the mechanisms of the distribution of nanoparticle-mediated transfection in the canine myocardium and that these 72 hours studies in dogs with an incision site just below the subtansverse which is a juncture of the reentry loop and conduction block in this region should limit or prevent inducibility of atrial flutter only as a determination of optimal nucleic acid vector deliver conditions (page 52). The strategy of this approach is to create a permanent conduction block in the right atrium that results in a re-entry loop for atrial impluses conduction for inducing atrial flutter (page 54). However, the *in vitro* function of a nucleic acid encoding defective HERG by PLGA/PLL nanoparticle delivery to cultured cells or section tissues does not provide a prediction of alleviating any disease or disorder such as re-entrant atrial flutter or arrhythmia as the results only pertain to the ability of delivery to dogs and *in vitro* analysis of gene expression in cultured cells. The specification fails to provide a correlation to a therapeutic levels of expression of nucleic acid encoding defective HERG (A561V) protein operably linked with a CMV promoter or cardiac tissue specific promoter in an *in vivo* setting in any subject having a re-entrant atrial flutter disorder or disease. The specification fails to even teach or provide guidance for what type of therapeutic effect with regards to alleviating atrial flutter or atrial fibrillation disorder

corresponds to alleviating atrial flutter by expressing defective HERG protein which may not be a prediction of therapy in an in vivo setting.

In general, in vitro gene expression is not representative of gene expression in a host subject whose cells (or target cells) have been somatically transfected in vivo. This is because numerous factors complicate in vivo gene transfer and expression which result in therapeutic effects. See Eck & Wilson ('Gene-Based Therapy' in The Pharmacological Basis of Therapeutics, 1996), who report the numerous factors complicate in vivo gene therapy with respect to predictably achieving levels and duration of gene expression which has not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. See page 82, column 1, first paragraph. These factors differ dramatically based on the vector used and the protein being produced, which cells are the target cells, and the disease and/or host being treated. It is further noted that Eck & Wilson support the importance of tailoring a gene therapy vector and methods to specific diseases and/ or disorders. See page 82, column 1, first paragraph. For example, Eck & Wilson et al. review the state of the art for gene therapy for inherited disorders and discloses that "[t]he level of protein

function necessary to achieve complementation of the defect varies widely among genetic diseases." See page 78, column 2, 2nd paragraph. However, the specification fails to teach the level of HERG (A561V) function necessary to achieve alleviating atrial flutter which provides therapy of any particular disorder. The specification fails to address how to overcome any of above unpredictable parameters in the gene therapy art such that one would be able to achieve therapeutic gene expression in target cells in a subject with atrial fibrillation or flutter. As such, with respect to the unpredictable nature of the gene therapy art, and particularly when taken with the specification's lack of any teaching of or sufficient guidance for defective HERG expression or any therapeutic gene expression in vivo, it is not predictable if defective HERG gene expression would start or continue in target cells or any cells at levels and for a duration which would be considered to be therapeutic in a subject to alleviate atrial flutter or any other disease/disorder since somatic gene delivery often results in only limited expression in inadequate numbers of cells, and most particularly since specification only provides a prediction of defective HERG gene expression cardiac myocyte cells in culture to correlate alleviating atrial flutter.

In particular regard to the claimed invention, it is further of interest to not that Kagan et al (The Journal of Biological Chemistry, 2000) report that the functions of HERG (A561V) protein have some unanswered questions such as specific identification of chaperones or processing proteins that may interact with newly forming HERG channels and whether cellular systems other than proteosome are involved and that there are an increasing number of LQT mutations

being described whose mechanisms of pathogenesis are yet to be investigated. See page 11247, column 2, 2nd paragraph. While Kagan et al supports that there may be some correlation between HERG (A561V) expression and reducing wild-type current density as predicted for a tetrameric assembly where one mutant subunit is sufficient to reduce functional activity nearly completely in cultured mammalian cells (page 11241, column 2, 2nd paragraph). Kagan et al do not provide any evidence that such expression levels in vitro would be correlative to achieving therapeutic effects in a subject to alleviate any disease or disorder by means of administration of nucleic acid encoding defective HERG protein to cells (or particular target cells) of the subject.

Note that the cited post-filing art clearly indicates an unpredictable status of the gene therapy art in a general sense as well as its specifically pertains to defective HERG gene expression. And, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a particular gene of interest (in this case defective HERG protein) which results in a therapeutic effect. As such, evidence pertaining to a specific vector, gene, promoter, route of administration, and therapeutic effect must be correlative to what is claimed, and in the instant application, a correlation or nexus cannot be drawn for the reasons discussed in the preceding paragraphs.

As for the animal model, the specification fails to provide the correlation between the dog model to any and all animal as claimed by the instant invention. With regards to extrapolating

from *animal* data of the specification to gene therapy of a disease, the importance of relevant animal models for support of enablement is imperative in the determination for effectiveness of gene therapy. This observation is supported by Orkin et al. in the "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" (see pages 10-11 and 14). On page 11, second and third paragraphs, Orkin et al emphasize the importance of relevant animal models, and state that many "mouse models often do not faithfully mimic the relevant human conditions." Orkin stress the importance of using relevant animal models for determining the effectiveness of therapeutic methodologies. Applicants specification does not provide any evidence that animal models available to the skilled artisan would provide a reasonable nexus to that of any and all animal condition to alleviating any and all diseases or disorders. Again, the example on pages 52-57 only teaches a dog with a "Y"-shaped lesion right atrial incision is at the inferior board of the atrium along the inferior vena cava to create a permanent conduction block in the right atrium that results in a re-entry loop for atrial impulse conduction for inducing atrial flutter.

Note also that the issue of "correlation" is dependent on the state of the art at the time of the invention. MPEP, section 2164 goes on to discuss that if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention broadly pertains, then there is lack of predictability in the art. Thus, what is known in the art provides evidence as to the question of predictability.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters listed above for achieving reverse gene therapy, the lack of direction or guidance provided by the specification to carry out defective HERG gene therapy as broadly claimed involving any and all vectors, promoters, target cells, and subjects, the absence of working examples for the demonstration or correlation to achieving alleviating any and all diseases or disorders such as atrial flutter and arrhythmia by the expression of any and all therapeutic nucleic acid such as defective HERG gene expression *in vivo*, the breadth of the claims directed to any and all vectors, promoters, target cells, and subject having any and all diseases or disorders, and the unpredictable and undeveloped state of the art with respect ot the gene therapy art as well as to the defective HERG (A561V) protein art for in vivo function, it would have required undue experimentation for one of skilled in the art to carry out the claimed methods.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22, 33 and 34-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is written in improper Markush language.

Claim 33 is vague and indefinite for claim 33 is dependent to itself. Note, claims 34-38 depend from claim 33.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 39 is directed to a vector comprising a promoter operably linked with a nucleic acid encoding a therapeutic gene product which is normally only expressed in cells of an abnormal tissue that is not afflicted with the disease or disorder.

Claim 39 is rejected under 35 U.S.C. 102(b) as being anticipated by Sanguinetti et al., Proc. Natl. Acad. Sci. USA (March 1996), Vol. 93, pages 2208-2212.

Sanguinetti et al teach HERG cDNA expression construct in the pSP64 transcription vector and site-directed mutagenesis was performed to determine the dominant-negative affect of mutations in HERG on HERG function (page 2208, Materials and Methods).

Conclusion

Claims 1-38 appear to be free of the cited prior art of record because the cited prior art of record fails to teach or suggest a method of alleviating a disease or disorder in an affected animal cell by locally delivering to the cell a reverse gene therapy vector comprising a promoter

operably linked with a nucleic acid encoding a therapeutic gene product which is usually only expressed in cells of abnormal tissue that is not afflicted with the disease or disorder, nor does the prior art teach or suggest alleviating a disease or disorder via reverse gene therapy, supra. However, the claims are subject to other rejections.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gai (Jennifer) Mi Lee, whose telephone number is 703-306-5881. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (EST). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Gai (Jennifer) Lee
Patent Examiner
Art Unit 1600

Patent Examiner
1632